NTP
National Toxicology Program

Studies Supported Through the Interagency Agreement with NCTR

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Disclaimer

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FDA

FDA Mission

- Protect public health by ensuring safety, efficacy and security of human and animal drugs, biological products, medical devices, food supply, cosmetics, and products that emit radiation.
- Advance public health by speeding innovations for more effective, safe and affordable medicines and food.
- Provide public with accurate, science-based information.

FDA

Products Regulated by FDA

Foods
- All interstate domestic and imported; including produce, fish, shellfish, shell eggs, milk; except meat and poultry.
- Bottled water.
- Wine (<7% alcohol).
- Infant formula

Food Additives
- Colors
- Food containers

Cosmetics

Dietary Supplements

Animal Feeds

Pharmaceuticals
- Human (safety, efficacy)
- Animal (safety, efficacy)

Medical Devices

Radiation Producing Devices

Vaccines

Blood Products

Tissues

Tobacco

Sterilants

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NCTR Mission

FDA's
National Center for Toxicological Research (NCTR, Jefferson, AR)

Conducts peer-reviewed scientific research in support of FDA mission, and provides technical expertise, for science-based regulatory decisions to improve health of US public:

- Understand critical biological events in toxicity;
- Develop and characterize methods and incorporate new technologies to improve assessment of human exposure, susceptibility and risk;
- Increase understanding of interaction between genetics, metabolism and nutrition.

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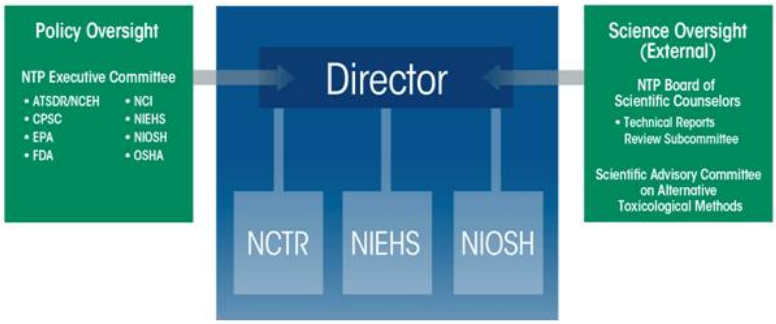
NTP Mission



- Evaluate agents of public health concern through development and application of tools of modern toxicology and molecular biology.
- Maintain an objective, science-based approach to critical issues in toxicology.
- Commit to using best science available.

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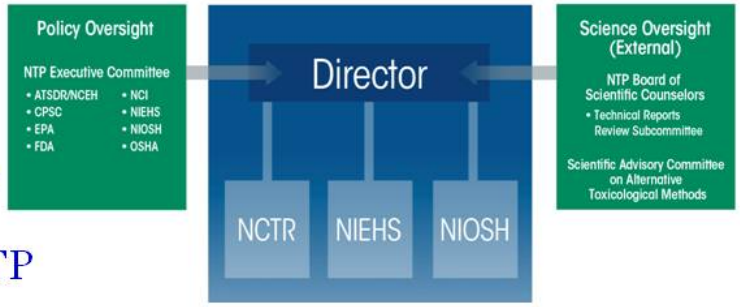
NCTR/FDA as NTP Partner

- NCTR/FDA, NIOSH/CDC, NIEHS founding organizations of NTP



- Representation on NTP Committees:
  - -Interagency Chemical Coordination and Evaluation Committee (ICCEC)
  - - Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - - Board of Scientific Counselors (BSC)
  - - BSC Technical Report Review Subcommittee
  - - Executive Committee

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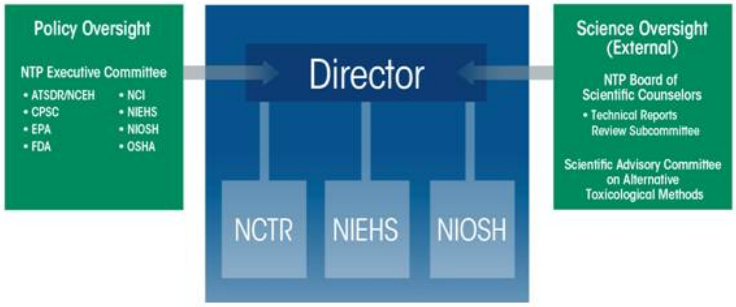
NCTR/FDA as NTP Partner



- NTP-related toxicological research projects ongoing at NCTR and within FDA.
- Peer-reviewed publications on toxicity, mechanism of action, or related toxicological methods.

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Interagency Agreement (IAG) between NCTR/FDA and NTP/NIEHS

- NTP and FDA interests "overlap" on toxicity of FDA-regulated products.
- Established Interagency Agreement (IAG) to facilitate cooperation between NCTR/FDA and NTP/NIEHS on compounds of mutual interest.

Initiated 10 Dec 1992

Dr. J.E. Henney (FDA) *Dr. K.L. Olden (NIEHS)*

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Goals of IAG

(1) Support the design and conduct of toxicological studies consistent with needs and goals of FDA and NTP/NIEHS.
(2) Provide oversight and ensure studies are conducted in the most rigorous scientific manner.
(3) Ensure data resulting from the studies are available to enable regulatory agencies (U.S. and worldwide) to make science-based, safety assessment and risk management decisions.

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Nomination/ Review Process - IAG

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Nomination Sources:

FDA

CBER CDER
CDRH CFSAN
CVM OC (ORA)

FDA CSWG

FDA

NTP

OCNS

ICCEC

Project Plan (Concept)

Concept Review

Board of Scientific Counselors BSC

Executive Committee

NTP Technical Reports

IAG

PI: Study Design

TSSRC

Study Execution

NCTR Final Report

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IAG Toxicology Study Selection and Review Committee (TSSRC)

(1) Oversight of studies on Interagency Agreement.

(2) **Provide forum for interaction between:**

NCTR study scientist,
FDA regulatory scientists,
NTP toxicologists

* *reiterative process with continuous input from regulatory scientists*

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IAG Toxicology Study Selection and Review Committee (TSSRC)

(3) Scientists from FDA, NTP/NIEHS, and invited subject matter experts.

(4) Biannual meeting.

(5) Protocol reviewed at FDA and NTP.

(6) Typical presentation/interaction:

30 min presentation by study scientist (concept; research plan; study progress)

Input from FDA regulatory center scientists

Input from other FDA center scientists

Input from invited scientists at meeting

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Compounds Studied - Areas

Endocrine Active Agents

Dietary Supplements

Food Contaminants & Food Safety

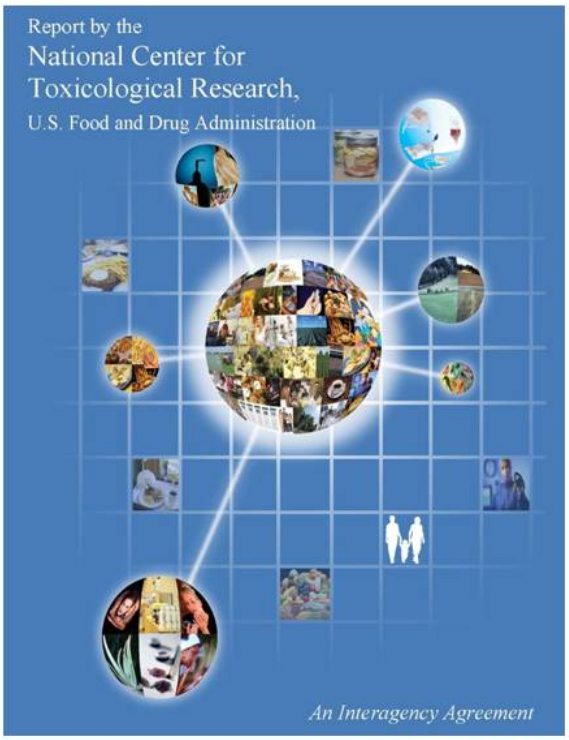
Pediatric/Translational

Drug/Device Interaction

AIDS Therapeutics

Phototoxicity

Nanoscale Materials



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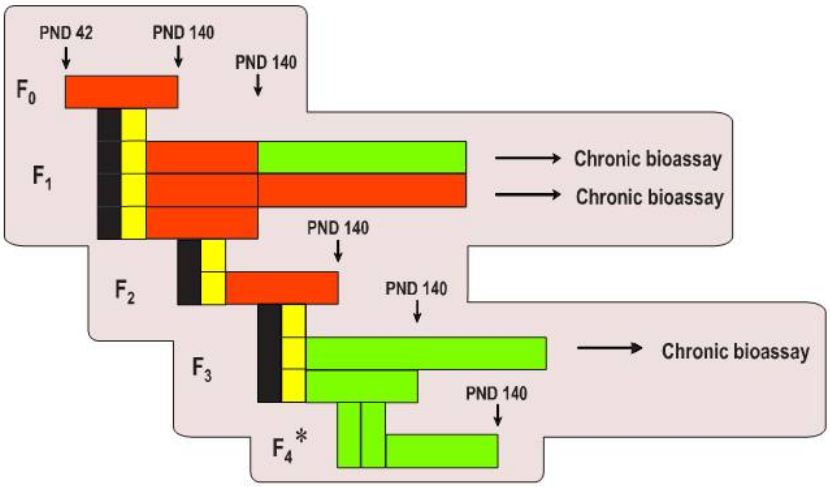
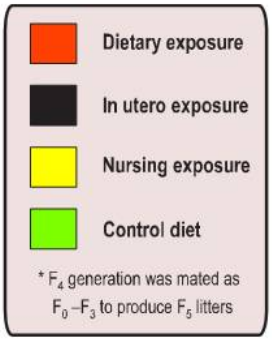
Endocrine Active Agents

Multigenerational Studies





Endocrine Active Agents

Multigenerational Studies

Genistein (TR-539, TR-545)

- Endocrine effects in exposed female and male SD rats; no generational amplification

Ethinyl Estradiol (TR-547, TR-548)

- Positive control for above studies; effects in female and male SD rats; no generational amplification

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Endocrine Active Agents

Endocrine Disruptor Studies

* Bisphenol A

- *pharmacokinetic study using rats and non-human primates for physiologically-based pharmacokinetic (PBPK) model*
- *subchronic toxicity in rats, targeted endpoints*
- *(neuroanatomy and behavior study in rats)*

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** on-going studies*

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Dietary Supplements

Riddelliine (mechanistic) (TR-508)

- Mechanistic studies identified common DNA reactive intermediate for pyrrolizidine alkaloids

† Aloe vera (oral)

- Determine dose-response following chronic oral administration of whole leaf

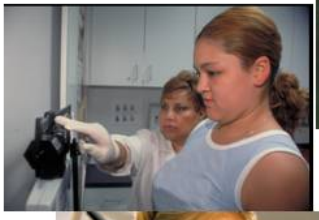
† to be reviewed at 2010 BSC TRRS meeting

Dietary Supplements

Ephedra

- Studies cancelled when FDA banned ephedra use in products.

* Bitter Orange (*Citrus aurantium*)



- Developmental toxicity studies

- Physiological effects in exercise challenged rat (± caffeine)

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** on-going studies*

Dietary Supplements

* Usnic Acid and *Usnea* lichen

- Toxicokinetics and mechanistic studies in vitro and in rats

* Glucosamine/Chondroitin Sulfate

- Toxicity in diabetic rat model

** on-going studies*

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Food Contaminants and Food Safety

Fumonisin B_1 (TR-496)

- Established hepato- and renal-carcinogenicity, non-genotoxic mechanism; dose-response for risk assessment

Malachite Green (TR-527)

- Established hepatocarcinogenicity; dose-response for risk assessment

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Food Contaminants and Food Safety

*† Acrylamide

- Conducting carcinogenesis, toxicokinetics, PBPK, neuroendocrine, neurotoxicity studies

* Furan

- Conducting carcinogenesis study in rats to examine lower end of dose-response curve

*on-going studies
† to be reviewed at 2010 BSC TRRS meeting

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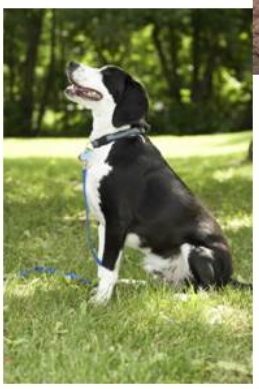
Food Contaminants and Food Safety

* Melamine plus Cyanuric Acid

- Establish dose-response in rodents and pigs; biomarkers and mechanism of action



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** on-going studies*

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Pediatric/Translational

Chloral hydrate (TR-502)

- Carcinogenesis in female mice was equivocal; neonatal exposure; mutagenicity studies equivocal

Chloral hydrate (dietary restricted) (TR-503)

- Liver carcinogenesis in dietary restricted mice through peroxisome proliferation

** on-going studies*

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Pediatric/Translational

* Ketamine

- Verify and quantify in vitro and in vivo (rat) neurological apoptosis effects; behavioral studies

* Di(2-ethylhexyl)phthalate

- Development of mechanistic and analytical methods for effects in rodents; pharmacokinetic studies in non-human primates

** on-going studies*

Drug/Device Interaction

Urethane +/- ethanol (TR-510)

-Ethanol had weak/mixed effect on urethane carcinogenicity

* Cellular telephone radiation

- Support NTP in vivo studies with brain histochemistry; in vitro studies

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** on-going studies*

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AIDS Therapeutics

† Combination of Zidovudine, Nevirapine, Lamivudine, Nelfinavir, and Efavirenz

- Quantify carcinogenesis with transplacental and transplacental/neonatal exposure; mechanism (DNA adducts, mutagenicity, clastogenicity)

† Zidovudine and Lamivudine in transgenic mouse model

- Determine carcinogenicity in genetically modified mouse model [C3B6F1$^{trp53(+/-)}$, FVBp16$^{Ink4a(+/-)}$/p19 $^{Arf(+/-)}$]

† *to be reviewed at Nov 2009 BSC TRRS meeting*

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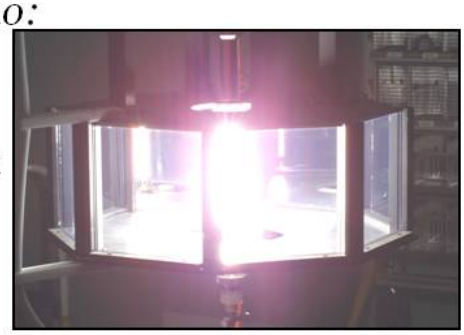
Phototoxicity

NTP Center for Phototoxicology

-Add "photo-" to NTP testing portfolio: phototoxicity, photocarcinogenesis, photococarcinogenesis, "photon-based" mechanism of action



- Simulated solar light, UVB, UVA, laser light

- Hairless mouse

- Transgenic mice

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Phototoxicity

Alpha and Beta Hydroxy Acids (TR-524)

- Determined that application of alpha hydroxy acid did not increase carcinogenesis of sunlight (photococarcinogenesis); beta hydroxy acid protected.

Aloe Vera (topical) (TR-553)

- Determined that application of aloe constituents to skin had marginal effect on carcinogenesis of sunlight.

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Phototoxicity

† Retinyl Palmitate

- Determine the photococarcinogenesis of topical application of RP

* Permanent Makeup Inks

- Determine the immunogenic component in permanent makeup inks that caused adverse events

Lemon and Lime Oil Furocoumarins

- Established DNA adduct of oxypeucedanin and other furanocoumarins

** on-going studies*

† to be reviewed at Nov 2009 BSC TRRS meeting

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Nanoscale Materials

* Titanium Dioxide and Zinc Oxide

- Determine if nanoscale materials penetrate skin; further studies if warranted

* Tg.AC Model with Titanium Dioxide

- Tg.AC model for phototumorigenicity; if warranted, photoactivation following nanoscale TiO2 application

** on-going studies*

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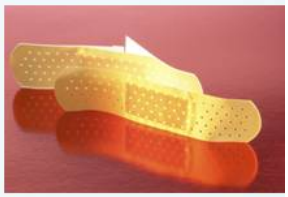
Nanoscale Materials



* Nanoscale Silver

- Determine pharmacokinetics; methods of measurement; subchronic toxicity and role of size and shape

* Nanoscale Gold

- Determine pharmacokinetics and subchronic toxicity

** on-going studies*

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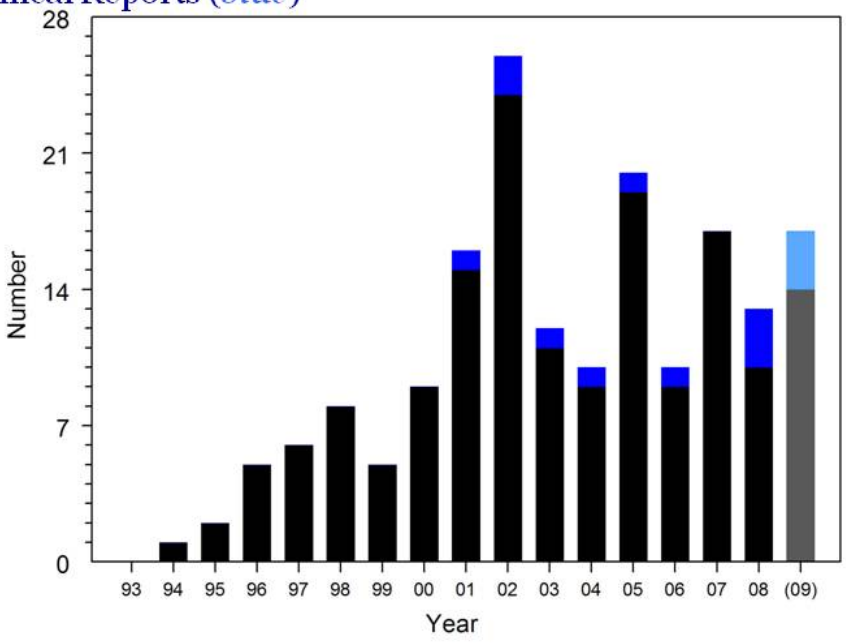
Output Measures of Interagency Agreement

Number of Peer-Review Publications (*black*),
or Technical Reports (*blue*)



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* Public Health Impact

- Fumonisin B_1 study established carcinogenicity; used to set US and WHO acceptable levels in human and animal food.
- Chloral hydrate studies led to FDA conclusion that pediatric risk was minimal and not requiring labeling changes.
- Urethane studies resulted in distilled spirits industry changing manufacturing methods to reduce levels.

** Selected examples*

FDA

* Public Health Impact

- Malachite green study established carcinogenicity; used to support continued ban on use with edible fish (US, UK).
- Riddelliine mechanistic studies indicated common active intermediate for pyrrolizidine alkaloids; FDA issued warning and established contaminant levels for pyrrolizidine alkaloids.
- Alpha- and beta-hydroxy acid studies resulted in FDA conclusion of no added risk in presence of sunlight.

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** Selected examples*

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Interagency Agreement between NCTR/FDA and NTP/NIEHS:

"A successful partnership protecting public health"